REMARKS

At the outset, Applicants wish to thank Examiner Sisson for taking the time to meet with Applicants' representative on August 16, 2005.

Claims 1-4 and 18-27 are pending. Claims 1-4 and 18-27 are rejected under 35 U.S.C. § 112, first paragraph and the specification is objected to. Applicants address each of these rejections as follows.

Claim Amendments

Claim 1 has been amended to be directed a fusion protein containing a first polypeptide including a ligand binding domain of a steroid hormone receptor and a second polypeptide including a G-CSF-receptor or a proliferation inducing domain thereof. In particular, the features of dependent claim 2 have been incorporated into claim 1. In view of this amendment, claim 2 has been canceled. Applicants submit that the instant amendment is commensurate with the comments set forth during the August 16th interview. No new matter has been added by the present amendment.

Objection to the Specification

The Office objects to the specification because of minor informalities. In particular, the last two pages of the disclosure include a listing of references with pages

numbered 1 and 2. In accordance with the Office's suggestion, Applicants submit herewith replacement sheets, labeled pages 16 and 17, respectively. This basis for objection should be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

The Office maintains the rejection of claims 1-4 and 18-27 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description and enablement requirements. According to the Office (page 5)

> [C]laim 1 has been interpreted as encompassing a vast genus of fusion proteins where each component of the fusion protein may comprise amino acid sequences corresponding to any like protein found in any life form, as well as conservative and non-conservative substitutions within each component of the fusion protein [and] ... deletion mutants.

The Office appears to focus on the fact that the components of the fusion protein are identified by name and function and the fact that amino acid sequences associated with such names and functionality are not provided in the specification. ("The specification has not been found to provide an adequate written description of any amino acid sequence that is associated with any of the stipulated functions or activities of the various components;" Office Action, page 6, point 9)

As an initial matter, as discussed in the personal interview, Applicants direct the Office's attention to the following related co-pending applications: (1) Divisional

Application Serial No. 09/905,592, containing claims directed to a vector encoding a fusion protein as presently claimed, and (2) Continuation-in-Part Application Serial No. 09/577,084 ("the '084 application"), containing claims directed to a fusion protein analogous to that claimed in the present application, where the second polypeptide includes c-mpl or a proliferation inducing part thereof. Applicants have noted certain inconsistencies with regard to the prosecution history, particularly in regard to reference and non-reference based grounds for rejection promulgated and maintained by the Office. For example, a written description and enablement rejection analogous to that set forth in the present Office Action was previously withdrawn in the '084 application. Accordingly, to ensure consistency of prosecution, Applicants respectfully request reconsideration and withdrawal of the instant rejection in light of the prosecution history of the related co-pending applications.

In addition, Applicants direct the Office's attention to a recent decision by the United States Court of Appeals for the Federal Circuit, *Capon v. Eshhar,* 03-1480-1481; Interference No. 103,887 (Fed. Cir. 2005); a copy of which is provided herewith and is labeled Appendix A. The *Capon* decision is based on an interference proceeding involving claims directed to chimeric genes for the production of membrane-bound proteins. The Board of Patent Appeals and Interferences ("the Board") rejected the claims of both parties under 35 U.S.C. § 112, first paragraph, noting that the claims

lacked an adequate written description in the specification. In particular, the Board concluded that the written description requirement necessitated a listing of the specific nucleotide sequences of the claimed DNA. On appeal, the Federal Circuit reversed, with the court stating (page 15):

> The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes. (emphasis added)

The written description requirement must be applied in the context of the particular invention and the state of the knowledge. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh.

The claims at issue in the *Capon* decision are substantially analogous to those at issue in the present application. Specifically, the disputed claims in *Capon* were directed to chimeric (i.e., fusion) genes encoding specific domain components defined in terms of their function and origin rather than their specific structure (e.g., a "DNA encoding a signal sequence," a "DNA encoding a transmembrane domain," etc.). The Board found the functional limitations to be insufficient, noting that controlling precedent required the inclusion in the specification of the complete nucleotide sequence of at least one chimeric

gene as well as reference to "structure, formula, chemical name, or physical properties" of the many protein domains, and/or DNA sequences which encode many protein domains referenced in the claims. As noted above, the Federal Circuit stated that "the Board erred in ruling that § 112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field."

Like the inventions of Capon and Eshhar, Applicants' invention does not lie in the discovery of particular protein domains associated with particular functions (e.g., ligand binding, dimerization, proliferation, etc.). Rather, the invention lies in the novel combination of known protein segments (i.e., domains) having known functions (e.g., ligand binding, proliferation signaling) to achieve a novel result (i.e., a fusion protein that imparts selective proliferation). In support of this assertion, Applicants submit herewith the following references, labeled Appendices B - D:

1. Appendix B: Fukunaga et al., "Expression Cloning of a Receptor for Murine Granulocyte Colony-Stimulating Factor," Cell 61(2), 341-350 (1990);
2. Appendix C: Fukunaga et al., "Functional domains of the granulocyte colony-stimulating factor receptor," EMBO J. 10(10):2855-65 (1991); and
3. Appendix D: Greene, et al., "Sequence and expression of human estrogen receptor complementary DNA," Science 231(4742), 1150-1154 (1986).

The Fukunaga reference of Appendix B conclusively establishes that the nucleotide and amino acid sequences of the G-CSF receptor, including the location of its extracellular and cytoplasmic domains, were known at the time of filing. Furthermore, the Fukunaga reference of Appendix C describes the identification and characterization of the functional domains of the murine and human G-CSF receptors, including the identification of the domain responsible for the transduction of the G-CSF triggered growth signal. Accordingly, contrary to the Office's assertion, the structure of the G-CSF receptor and its proliferation inducing domain were known at the time of filing and, therefore, following the principles enumerated in the *Capon* decision, need not be reiterated, described, or reproduced in the instant specification in order to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Similarly, the Greene reference of Appendix D establishes that the amino acid sequence of the human estrogen receptor and the human glucocorticoid receptor was known at the time of filing. Greene further identifies the homologous region, which is rich in cysteine, lysine, and arginine, as the DNA-binding domain of these proteins. Accordingly, as the structures of steroid hormone receptors and their ligand binding domains were known in the art at the time of filing, they need not be described in Applicants' specification.

Like the Office in the present case, Director Dudas in *Capon* questioned whether the specifications adequately supported the breadth of the claims presented (e.g., including conservative, non-conservative and deletion mutants), noting "that it cannot be known whether all of the permutations and combinations covered by the claims will be effective for the intended purpose, and that the claims are too broad because they may include inoperative species" (page 16). The court, citing to *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976), countered that "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. The Federal Circuit reasoned (page 17):

> While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. Both Eshhar and Capon present not only general teachings of how to select and recombine the DNA, but also specific examples of the production of specified chimeric genes.

Like Capon and Eshhar, Applicants have presented not only general teachings of how to select and recombine the polypeptides recited in the present claims, but also provided specific examples of the production of the presently claimed fusion proteins (see, in particular, Examples 1 and 4, of the specification). Here Applicants teach construction of genes encoding fusion proteins such as those encompassed by the present claims. Further, as taught, for instance, in Example 2, cells expressing a chimeric protein

containing the entire G-CSF receptor and the ligand-binding domain of the estrogen receptor showed estrogen-dependent proliferation. Further, Example 2 teaches that "[t]he production of the desired fusion protein in the cells was confirmed by western blotting." As such, Applicants submit that the specification clearly describes the fusion proteins encompassed by the present claims. For all the above reasons, Applicants submit that the present specification need not set forth the nucleotide or amino acid sequences of known polypeptides that are included in the presently claimed fusion protein to satisfy the written description requirement. This basis for the § 112, first paragraph, rejection should be withdrawn.

Turning to the issue of enablement, the Office again points to *Genentech v. Novo Nordisk A/S,* 108 F.3d 1361, 42 U.S.P.Q.2d 1001(Fed. Cir. 1997) in support of the assertion that the present claims are not enabled by the specification as filed. However, as noted in the Applicants' response of November 7, 2002, Applicants respectfully submit that the two situations are distinct. The *Genentech* case involved a claim to a process of expressing a DNA encoding a conjugate protein and using an enzyme to cleave off an undesired portion of that protein, a process generally known as cleavable fusion expression. One of the questions before the court was whether the specification would have enabled a person having ordinary skill in the art at the time of filing to use cleavable fusion expression to make hGH without undue experimentation. The accompanying

specification did not describe *in any detail whatsoever* how to make hGH using cleavable fusion expression. The court found the lack of enabling detail to be fatal.

The instant case is fundamentally different. Unlike the *Genentech* application, whose disclosure was limited to general instructions and prophetic examples, the present application not only provides ample description of the methods for making and using the fusion proteins at issue, but the invention was also reduced to practice a number of times.

On this point, the Office's attention is directed to Examples 1 and 4, which are working examples that describe the construction of three selective amplification fusion genes of the present invention - GCRER, GCRΔ(5-195)/ER, GCRΔ(5-195, 725-726)/ER, alone and ligated with IRES-CD24. Other examples in the specification describe, in sufficient detail to enable one of ordinary skill in the art to replicate the results obtained, the introduction of the fusion genes into cells and the expression of fusion proteins (see, e.g., Example 2) and the use of the expression of such fusion proteins to enable selective amplification of transformed cells (see, e.g., Examples 3 and 5). Applicants submit that these examples are sufficiently detailed to allow one of ordinary skill in the art to make and use the claimed invention.

The Office also asserts that "no reaction conditions, dosages, therapy regimens, etc. are provided" (page 12). For the reasons noted above, Applicants submit that how to make and use fusion proteins encompassed by the present claims and having the required

function is enabled by the application as filed. The Office needs to establish a reasonable basis to question the enabling nature of Applicants' specification with regard to the presently claimed fusion proteins. In a case in which the Office questions the enablement of a claim, the Circuit Court for Patent Appeals, in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367, 369 (CCPA 1971) has stated that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis added).

The M.P.E.P. (§ 2164.04, Eighth Edition, Rev. 2, May 2004) further emphasizes the *Marzocchi* standard in stating that:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure (emphasis added).

In the absence of evidence or reason for doubting Applicants' teaching on making and using the fusion proteins encompassed by the present claims, Applicants submit that the § 112, first paragraph enablement rejection should be withdrawn.

In sum, Applicants respectfully submit that the specification as filed, taken in conjunction with that which is known in the art, not only provides an adequate written description of that which is now claimed but also enables one skilled in the art to make and use that which is now claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the pending rejections in view of the remarks presented herein as well as those set forth in Applicants' prior responses.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including September 23, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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